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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	018743/0276324	1864

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,13,15-18,21,23,24,28,29,32,40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,13,15-18,21,23,24,28,29,32,40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 6-8, 13, 15-18, 21, 23, 24, 28, 29, 32, and 40 are pending.

Election/Restrictions

The non-elected species in claims 16 and 32 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/15/01.

Claim Objections

Claims 8 and 17 remain objected to because of the following informalities:

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim, which depends from a dependent claim, should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

If and when claims 8 and 17 are in condition for allowance they will have to renumbered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "The method of claim 31" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claims is not further treated on its merits because the examiner cannot determine what claim, claim 32 should depend from.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13, 15-18, 21, 23, 29, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (US 6,251,957) taken with Conti-Fine (US 6,929,796). A method of inhibiting in a mammal formation of neutralizing antibodies directed against a virus comprising the step of co-administering to said mammal said virus and a combination of immune

modulators which inhibits neutralizing antibodies against said virus, wherein the combination of immune modulators consists of cyclophosphamide and an anti-CD4 monoclonal antibody (columns 25-26). Wilson teaches a gene therapy method comprising co-administering with a viral vector comprising a heterologous nucleotide sequence and an immunosuppressive agent to a human (column 2, lines 35-52, column 4, lines 20-34 and column 25-26). Wilson teaches that the viral vector can be AAV (column 26). Wilson teaches that an immune response can be the product of the transgene when that transgene expresses a protein that is foreign to the treated host (column 1). Wilson teaches that the immunosuppressive agent may be administered prior to or concurrently with the recombinant viral vector (column 2, lines 45-49). However, Wilson does not specifically using the method to inhibit or prevent inhibitory antibodies against the protein being provided via gene therapy, wherein the protein is encoded by a heterologous nucleotide sequence that is from the same species as said mammal.

However, at the time the invention was made, hemophilia mammals that do not produce factor VIII or Factor IX, but produce anti-factor VIII or anti-factor IX antibodies after exogenous administration of factor VIII or IX were well known to one of ordinary skill in the art as exemplified by Conti-Fine (columns 3-6 and 15). Conti-Fine further teaches one of ordinary skill in the art would want to use an immunosuppressive agent in combination with gene therapy to inhibit antibodies against the protein(s) because the protein or viral proteins are foreign to the subject and the subject would develop an immune response to these proteins (columns 6-7). Conti-Fine teaches a method of inhibiting or preventing inhibitory antibodies to Factor IX in a subject (e.g., humans) comprising administering an immunosuppressive agent, wherein the Factor IX is delivered via gene therapy to the subject (abstract and columns 3-7, 14-15, and 30).

The gene therapy to the subject (e.g., human) comprising administering viral vector comprising Factor IX being from the same species as the subject (columns 4-6 and 14-15). The viral vector can be an adeno associated viral vector (columns 6, 15, and 27).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine, namely to use a gene encoding a protein from the same species as the species being treated in the method. One of ordinary skill in the art would have been motivated to combine the teaching for a reasonable expectation that the protein derived from the same species treated would have similar properties. See Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine, namely to use a gene encoding a coagulation protein (e.g., Factor IX or Factor VIII) in the method. One of ordinary skill in the art would have been motivated to combine the teaching to treat hemophilia.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine, namely to use cyclophosphamide to reduce inhibitory antibodies to the blood coagulation protein. One of ordinary skill in the art would have been motivated to combine the teaching to reduce inhibitory antibodies against the protein being expressed via gene therapy because an immune response can be from expression of a protein (e.g., Factor IX) that is foreign to the host.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine, namely to use

an adeno associated viral vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching for long-term expression of the protein.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine, namely to use a mammal having no detectable endogenous expression of the coagulation protein delivered in the method. One of ordinary skill in the art would have been motivated to combine the teaching to treat the mammal that does not express a coagulation protein (e.g., mammal with hemophilia A or B).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/26/06 have been fully considered but they are not persuasive.

In view of the lengthy prosecution history of the instant application, the majority of applicant's arguments have already been addressed in previous office actions (office action mailed on 7/25/05, 7/29/04, 1/9/04, 6/5/02).

In response to applicant's argument that in view of the art of record, there was no reasonable expectation of success to practice the claimed method, the argument is not found persuasive because the claimed invention embraces administering cyclophosphamide before gene therapy. Thus, the prior art only need to teach the step in claims 13, 16, 18, 21, and 23 directed to delivering cyclophosphamide to a mammal having a genetic defect resulting in generation of inhibitory antibodies to a blood coagulation protein. See pages 7-8 of applicant's arguments filed on 1/27/06.

In addition, with respect to administering cyclophosphamide with gene therapy and observing reduction of the formation of inhibitory antibodies, the claimed methods embrace any observation in reduction (including the reduction of one inhibitory antibody in the mammal) in the formation of inhibitory antibodies. One of ordinary skill in the art would have a reasonable expectation of success because the prior art of record teaches the reduction of inhibitory antibodies using cyclophosphamide (see Trapnell, pages 36-37). Tengborn teaches inhibitor level declined in one of the patients using cyclophosphamide (page 56). MPEP 2143.02 recites: "Obviousness does not require absolute predictability, however, at least some degree of predictability is required." Furthermore, "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." See In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). "When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability." In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).

In response to applicant's argument that the prior art of record teaches away from practicing the claimed method, the argument is not found persuasive for the reasons set forth above.

Claims 1-4, 6-8, 24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson taken with Conti-Fine as applied to claims 13, 15-18, 21, 23, 29, and 40 above, and further in view of Trapnell et al. (cited on a PTO-892).

Wilson taken with Conti-Fine do not specifically teach intravenously or intraperitoneally (IP) administering cyclophosphamide to the mammal.

However, at the time the invention was made, Trapnell teaches IP administering cyclophosphamide in combination with gene therapy (pages 33-38). Trapnell teaches that high doses of cyclophosphamide result in no detectable antibodies against the adenoviral vector (pages 36-37).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wilson taken with Conti-Fine in further view of Trapnell, namely to intraperitoneally administer cyclophosphamide to the mammal. One of ordinary skill in the art would have been motivated to combine the teaching to neutralize antibodies in the mammal. Furthermore, one of ordinary skill in the art would have a reasonable expectation of success for practicing the claimed method because Trapnell teaches that high doses of cyclophosphamide result in neutralizing antibodies. "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. See In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/26/06 have been fully considered but they are not persuasive for the reasons set forth in the prior art rejection.

With respect to applicant's argument directed to the unexpected result of preventing the formation of inhibitory antibodies to a blood coagulation factor delivered to a mammal by way of gene therapy observed in the specification, the argument is not found persuasive because

Trapnell teaches that high doses of cyclophosphamide resulted in no detectable antibodies (pages 36-37). See In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Douglas Schultz, PhD, SPE – Art Unit 1635, can be reached at (571) 272-0763.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman